June 6, 1956

Dr, Norman Horowitz
Caltech
Pasadena 4, Calif.

Dear Norman:

Thank you for your letter of the 4th. It is not hard to see why the penicillin-sensitive strains are gone, but I hoped you might have kept the collection of temperature-mutants that you and Leupold had amassed, in which some of the p.-s. strains are included. I am not sure I made this clear; the strains are cited in Rowley's paper. I will write to Rowley if you think he is back in London.

As to your counter-comments, I wish we could do this in extenso, in person, because we could spend days exchanging letters. I am sure you will compensate for the circumstances under which my comment was prepared; the written version follows the transcript rather closely, and did not have the benefit of the transcripts of the principal's remarks. For that reason, the "critique" that I felt was expected of me had to be directed at what I understood as a general background of discussion one the 1:1 theory, plus whatever specific remarks of your own I could assimilate on the spot. I am sorry if I have misattributed views to you that you do not share (and am pleased to see the very large area that we agree on.) On rereading my account, it does not seem that any specific statements were attributed to you, and my criticisms were certainly intended to be directed at what I consider a rather generalized erroneous formulation, and not to any personalities. The idea of a gene making an enzyme is stated fairly explicitly in a number of older papers (Beadle-Chem Rev 45; Tatum & Beadle [Ann Mo Bot Gard 46?; PNAS 1941;) and while Emerson ] these may no longer be representative of your own views, you have to take account of the usual cultural lag. The main point I want to stress is that the real answers on mechanisms of gene-enzyme relationships are not likely to come from genetic experiments.

I am afraid that I am at fault for evoking part of your criticism by overlooking a typographical error until just now. At p. 167, line 6 up, my ms. had read "experimentally indefeasible", but I missed the error in proof, so it's my own fault. I don't know whether the correct version is more congenial to you; it should be more intelligible. I was not terribly clear about the different levels on which the theory can be used. As a purely empirical matter, one can ask whether there are any apparent enzyme-pleiotropisms; there are quite a few in E. coli, and you have contributed some yourself, but the experiments you and Yanofsky cited seem to be the first concerted efforts to find specific examples in Neurospora. But at a deeper level, the theory is indefeasible because you could always explain away any exceptions by considering them to be secondary effects: inhibitors; quantitative levels, etc. Here we are in agreement, that the only plausible way to do genetic experiments is to assume a single primary effect: in fact why don't

just go ahead and postulate an ultimate unit of function which we can call a "physiological gene" regardless of its behavior in recombinational and mutational analysis. It would be impossible to disprove such a postulate. I do not consider that the evidence favors identification of the "physiological" gene with the units of crossing-over or of mutation, and it is misleading to promulgate the theory in such a form as to encourage the expectation that mutations with a given physiological effect must be allelic, or that mutations with manifold effects must be separable into physiological units by crossing-over. In view of your own comments, I am obviously beating a dead horse, except that there are some biochemists who still don't know that yet. if not by developmental analysis.

Sincerely,

Joshua Lederberg